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| EXAMINER | |
|---|---|
| KOSSON, ROSANNE | |

| ART UNIT | PAPER NUMBER |
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| 1652 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/563,360 | JANNES ET AL. | |
| | Examiner | Art Unit | |
| | Rosanne Kosson | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6,7,9-11,13,17,35,38,40,49,50,115 and 130-134* is/are pending in the application.

4a) Of the above claim(s) *10,11,13,17,35,38,40,49,50 and 115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,9,130 and 131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicants' election with traverse of Group I, claims 1-4, 6, 7, 9, 130 and 131, in the reply filed on October 12, 2007 is acknowledged. Claims 10, 11, 13, 17, 35, 38, 40, 49, 50, 115 and 132-134 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 5, 8, 12, 14-16, 18-34, 36-37, 39, 41-48, 51-114, 116-129 were canceled in a previous amendment. No claims were amended, canceled or added in response to the restriction requirement. Accordingly, claims 1-4, 6, 7, 9, 130 and 131 are examined on the merits herewith.

In reply to Applicants' traversal, Applicants appear not to understand or not to accept the rules and criteria for unity of invention, which were discussed clearly in the previous Office action. See PCT Rules 13-13.2 and 37 CFR §1.475. To reiterate, for unity of invention to be found, what is considered is the technical feature that is common to all of the groups of inventions presented. If this common technical feature is special, i.e., novel and not obvious, the different groups of inventions will be considered to have unity. But, in Applicants' case, the technical feature that links all of the groups of inventions is t-PA, and this common technical feature is well known in the art and, therefore, not novel and not special. Consequently, the different groups lack unity of invention.

Applicants note that the different inventions are drawn to different methods of identifying subjects that are predisposed to different diseases and to different polynucleotides, but they have not presented any other technical features common to all of groups of inventions.

Regarding rejoinder at the time of allowance, Applicants appear to refer to rejoinder under the doctrine of In re: Ochiai. This doctrine, however, pertains to rejoining methods of

making and using a particular product if claims to the product are allowable and if the method claims are of the same scope. But, Applicants have elected a method, a diagnostic screening method. Thus, this doctrine does not apply to the instant case.

In view of the foregoing, the restriction requirement is deemed proper and is made final.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 9, 130, and 131 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite a method of identifying a subject predisposed to ischemic stroke, comprising identifying any mutation in the subject (presumably in the genome of the subject) that reduces the release of t-PA. But, the specification discloses only such mutation, the C-to-T mutation at position –7351/2228 of the t-PA locus. Thus, the specification claims a vast genus of mutations but discloses only one species of this genus. This disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of genetic mutations may be achieved by a recitation of structural features common to each member (species) of the genus, **which features constitute a substantial portion of each member of the genus**. Because only one species is disclosed, it cannot be determined what the structural features that constitute a substantial portion of each

species in the genus are, as they are not disclosed in the specification. For example, do the mutations have to be located within a certain number of nucleotides of the t-PA gene? Do the mutations have to be of a particular type, i.e., of a particular length or of particular base substitutions? The specification does not define the structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Consequently, there is no evidence that a sufficient number of representative species of this large genus were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Because only one species of the claimed genus is disclosed, the claims fail to satisfy the written description requirement.

Claims 1-4, 6, 9, 130, and 131 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a subject predisposed to ischemic stroke, comprising identifying the C-to-T mutation at position –7351/ 2228 of the t-PA locus in the subject, does not reasonably provide enablement for a method of identifying a subject predisposed to ischemic stroke, comprising identifying any mutation in the subject (presumably in the genome of the subject) that reduces the release of t-PA. As a result, the specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the

nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

The claims are very broad because they recite a method of identifying a subject predisposed to ischemic stroke by identifying any mutation in the subject that reduces the release (i.e., reduces the amount or level of expression) of t-PA.

2. The nature of the invention.

The invention is designed to provide a novel diagnostic screening method for identifying people who have an increased risk of ischemic stroke.

3. The state of prior art.

See the discussion below of Kluft et al. (WO 97/07240 A1) and Bulens et al. ("Rentinoic acid induction of human tissue-type plasminogen activator gene expression via a direct repeat element (DR5) located at –7 kilobases," J Biol Chem 270(13):7167-7175, 1995).

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

Applicants have identified only one point mutation that may be used in the claimed method. As discussed below, Kluft et al. have identified two other mutations that may be used

in the claimed method. As discussed below, Bulens et al. have identified the genomic polynucleotide sequence upstream of the t-PA gene as containing regions that are critical to or important for t-PA expression. Thus, Bulens et al. suggest that mutations in this area are likely to affect or decrease t-PA expression. But, the claims read on identifying mutations throughout the human genome, or any animal genome, for use in the claimed method. It cannot be predicted that mutations that are linked to decreased t-PA expression are present throughout the entire genome of an animal.

6. The amount of guidance present.

Applicants have provided guidance for identifying people who are at an increased risk for ischemic stroke by virtue of having one mutation- a mutation in the 5' flanking region of the t-PA locus, the C-to-T mutation at nucleotide position 2228 (or –7351, depending on the numbering scheme used). But Applicants have provided no guidance to the effect that identifying any other mutation correlates with an increased risk of ischemic stroke.

7. The existence of working examples.

Applicants' guidance is presented in a working example.

8. The quantity of experimentation necessary.

To prove that identifying any mutation that decreases the rate of release of t-PA (amount or level of expression of t-PA) identifies an individual at increased risk for ischemic stroke, many experiments would have to be conducted under a wide range of conditions. In these experiments, the entire genomes of all types of animals that produce a t-PA would have to be screened for mutations, mutations would have to be identified relative to a standard for each type of animal tested, and each mutation would have to be studied to determine whether or not it is linked to decreased t-PA expression or activity. If such a relationship is found, subjects having each mutation would have to be studied to determine whether or not this mutation

correlates with an increased incidence of thrombotic vascular occlusions or ischemic stroke. For improved results, subjects who are homozygous and heterozygous for each mutation would have to be studied. These experiments would require an infinite amount of random screening, testing and data analysis.

These types of experiments and data are missing from the specification. A great deal of experimentation is needed to establish that any mutation may be associated with decreased t-PA expression and with an increased risk for ischemic stroke, because these this mutation is recited in the claims although only one such mutation is disclosed in the specification. Even if one such mutation could be identified, by random, trial-and-error screening and testing, without a very large amount of data, such a result could not be expected with a different mutation, particularly when tested in a different assay, or under different assay conditions, than the first mutation or when found in a different animal.

In view of the foregoing, the claims fail to satisfy the enablement requirement.

Claims 1 and 131 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a subject at increased risk for ischemic stroke (by identifying that his rate of release of t-PA is reduced), does not reasonably provide enablement for a method of identifying a subject in whom ischemic stroke can be prevented or treated. Treatment for stroke occurs after the stroke has happened, and Applicants have not demonstrated that stroke is a preventable disease, certainly not by the step of identifying a reduced "rate of release," i.e., level of expression of t-PA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is

required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of

factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

The claims are very broad because they recite a method of identifying a subject in whom ischemic stroke can be prevented or treated by identifying in that subject a reduced rate of t-PA (tissue plasminogen activator) release (i.e., a reduced level of t-PA expression).

2. The nature of the invention.

The invention is designed to provide a novel diagnostic screening method for identifying people who have an increased risk of ischemic stroke.

3. The state of prior art.

See the discussion below of Kluft et al. (WO 97/07240 A1) and Bulens et al. ("Rentinoic acid induction of human tissue-type plasminogen activator gene expression via a direct repeat element (DR5) located at –7 kilobases," J Biol Chem 270(13):7167-7175, 1995).

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

As discussed below, as well in the references submitted in Applicants' IDS, the prior art discloses that various mutations in the t-PA gene or in the 5' flanking region for the t-PA gene are associated with an increased incidence of thrombotic diseases, i.e., diseases caused by vascular occlusions. Thrombotic diseases include heart attack and stroke. But, the prior art

does not disclose that detecting one of these genetic mutations (recited very broadly in the claims as a method of identifying a reduced rate of release of t-PA in a subject) is a method of identifying a subject in whom a type of stroke can be prevented or treated. Detecting a risk factor for a disease does not treat or prevent that disease, particularly as treatment for stroke occurs after the subject has suffered a stroke. Treating the damage caused by the stroke does not depend on whether or not the subject has a particular genetic mutation, as anyone who has had a stroke is treated for the damage caused by the stroke. Also, stroke is a disease for which the likelihood of occurrence may be reduced, but it is not preventable.

6. The amount of guidance present.

Applicants have provided guidance for identifying one mutation in the 5' flanking region of the t-PA locus, the C-to-T mutation at nucleotide position 2228 (or –7351, depending on the numbering scheme used). Applicants have provided guidance for identifying people who are at an increased risk for ischemic stroke by virtue of having this mutation. But Applicants have provided no guidance to the effect that identifying this one mutation, or simply identifying a reduced level of t-PA in a subject, as recited in the claims, identifies a subject in whom stroke can be prevented or treated. Treating stroke entails the administration of a therapeutic composition or procedure to reduce or remove the thrombus or occlusion (or to inhibit or reduce vascular rupture or bleeding, or to provide rehabilitation to the patient). Preventing stroke entails the administration of a therapeutic composition or procedure with the result that stroke does not occur in any subject who receives the preventive measure. Treatment and prevention methods for a disease are distinct and separate from a risk factor screening method. Additionally, as note above, treatment for stroke is related to having had a stroke, not to having a particular genetic mutation in or near the t-PA gene, and any stroke victim for whom the stroke was not fatal can be treated.

7. The existence of working examples.

Applicants have no working examples disclosing the treatment or prevention of ischemic stroke in any subjects.

8. The quantity of experimentation necessary.

To prove prevention of any disease, including ischemic stroke, many experiments would have to be conducted under a wide range of conditions. In these experiments, to demonstrate prevention, many individuals would have to be identified who have a reduced level of t-PA (a reduce rate of release of t-PA). These individuals, of both genders, would have to represent a wide variety of people with respect to age, ethnic background, life style, diet, weight, overall health and specific diseases or risk factors (e.g., the condition of the heart, vasculature and blood, the history of strokes and heart attacks, the presence of diabetes, high cholesterol, high blood pressure, etc.). Matched cohorts for all of these subjects, subjects with all the same characteristics but a normal level of t-PA would have to identified. All the subjects would have to be followed over a period of time, and the prevention of ischemic stroke in all of the subjects would have to be ascertained. The essential element towards the validation of a preventive therapeutic measure is the ability to test the therapeutic measure on healthy subjects and affected subjects and *link* those results with subsequent biological or medical confirmation in the presence and absence of disease- in the instant case, confirmation of no ischemic stroke whatsoever. This irrefutable link between antecedent use of a therapeutic measure (identifying a reduced level of t-PA) and subsequent knowledge of the prevention of a disease is the essence of a valid preventive measure. Further, a preventive method or measure also must assume that it is safe and tolerable for anyone.

This type of experiment and data are missing from the specification. A great deal of guidance is needed to establish prevention because the claims recite identifying a subject in

whom stroke can be prevented by identifying a reduced level of t-PA in that subject. Even if the claimed method could identify one subject in whom stroke was prevented, without a very large amount of data, such a result could not be expected in a different subject, and certainly not if the second subject had different personal characteristics and health characteristics than the first subject.

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 7, 9, 130 and 131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the steps of determining the rate of release of t-PA in a subject and identifying a subject having a reduced rate of release of t-PA. Based on the specification and the prior art cited in Applicants' IDS, Applicants appear to mean the steps of determining the amount of t-PA, or the level of t-PA expression, in a subject and identifying a subject having a reduced amount or level of expression of t-PA compared to a normal subject, particularly as Applicants' invention appears to be the discovery of a point mutation associated with a decreased level or expression of t-PA, as measured in cell culture experiments. Appropriate correction is required. If Applicants' finding is that individuals having the C-to-T mutation at position –7351/2228 produce a normal amount of t-PA, but the mutation blocks the secretion of t-PA across cell membranes or the entry of t-PA into the cardiovascular system (i.e., if the mutation is involved in the mechanism of release of t-PA into the cardiovascular system), Applicants are invited to explain their findings and clarify this point.

Additionally, claim 130 recites the step of identifying a mutation in a subject. Applicants

appear to mean the step of identifying a mutation in a gene in the genome of a subject.

Appropriate correction is required.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 6, 9, 130 and 131 rejected under 35 U.S.C. 102(b) as being anticipated by Kluft et al. (WO 97/07240 A1). Kluft et al. disclose that vascular blood clots are the cause of diseases such as heart attack, cerebral infarction (ischemic stroke) and thrombi in veins. T-PA is a serine protease that degrades these clots, and t-PA is administered as a therapeutic agent to treat these diseases (see p. 1, first two paragraphs). Kluft et al. disclose that assaying the level or the activity of t-PA in plasma is difficult to perform accurately and that these data do not correlate with the incidence of thrombotic disease. A more accurate approach is to identify abnormal genotypes, which are reliably and easily measured and not influenced by external factors (see p. 3). Kluft et al. identified two mutations that are Alu inserts in the t-PA gene, one in intron h and one in exon IX, that cause t-PA deficiency (i.e., a reduced rate of t-PA release, as what is not made is not released) and that correlate with an increased incidence of heart attack. Kluft et al. note that their work provides a diagnostic method and a diagnostic kit for identifying individuals who have an increased risk of diseases associated with thrombus formation, such as cerebral infarction (see pp. 4, 5, 12 and 13). For the intron h insertion mutation, Kluft et al. determined whether the mutation was present in one or both alleles of the t-PA locus (see pp. 15-16 and Table 2 on p. 21). Kluft et al. disclose that the presence of the

genetic mutation can be detected by hybridization to a polynucleotide linked to a reporter or label moiety (see paragraph bridging pp. 6-7 and p. 12, line 24, to p. 13, line 2).

In view of the foregoing, a holding of anticipation is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 9, 130 and 131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kluft et al. (WO 97/07240 A1) in view of Bulens et al. ("Rentinoic acid induction of human tissue-type plasminogen activator gene expression via a direct repeat element (DR5) located at –7 kilobases," J Biol Chem 270(13):7167-7175, 1995).

The teachings of Kluft et al. are discussed above. Kluft et al. do not disclose that the type of stroke that people with mutations in or near the t-PA gene are at risk for is lacunar stroke. Kluft et al. do not disclose that the t-PA mutation is located upstream of the t-PA gene.

Bulens et al. have studied the human polynucleotide sequence upstream of the t-PA

gene and disclose several regions that are necessary for normal t-PA expression, regions that have promoter or enhancer activity. Deletion of one of these regions yields decreased t-PA expression. One of these regions, known as ER8, is located at nucleotide positions –7325 – -7535 (see p. 7170 and 7171, left col.), a region that includes the mutation found by Applicants at position –7351. One of ordinary skill in the art would have known that when a polynucleotide region that functions in expression is deleted, that deletion is likely to result in decreased expression. It would have been obvious to one of ordinary skill in the art at the time of the invention to identify subjects having a mutation in the genomic area upstream of the t-PA gene in order to identify those with a reduced amount or level of t-PA and who, therefore, have an increased risk of ischemic stroke, because Bulens et al. disclose that this upstream region is important for t-PA expression, while Kluft et al. disclose that individuals with reduced levels of t-PA expression are at a higher risk for thrombotic diseases such as ischemic stroke.

Regarding claim 2, which recites that the stroke is lacunar stroke, a stroke occurring due to blockage of a smaller blood vessel, one of ordinary skill in the art at the time of the invention would have known that a thrombotic occlusion that is not degraded by t-PA and that then causes a stroke may occur anywhere in the vasculature of the brain. One of ordinary skill in the art also would have known that small blood vessels can clog more easily than larger ones because of their smaller inner diameter, i.e., a thrombus of a particular size that clogs a smaller vessel may not clog a larger one. Further, one of ordinary skill in the art would have known that If a person produces a decreased amount of t-PA due to a genetic mutation, this person is at an increased risk for stroke of all types. Therefore, this claim does not render the claimed method patentable.

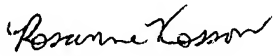
In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652 

rk/2007-10-26

/Rebecca Prouty/
Primary Examiner
Art Unit 1652